

(i) a first polypeptide comprising a HECT E3 ubiquitin ligase WW domain; SEQ ID NO:1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, or a variant thereof in which the ability of the polypeptide to bind to a Smad protein is not substantially diminished relative to the HECT E3 ubiquitin ligase;

cnf  
a,  
(ii) a second polypeptide comprising a Smad PY motif; SEQ ID NO:14, 15, 16, 17, 20, 21, 22, 23, 24, or 25, or a variant thereof in which the ability of the polypeptide to bind to an E3 ubiquitin ligase is not substantially diminished relative to a native Smad protein comprising the PY motif; and

(iii) a candidate agent; under conditions that permit a detectable level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent;

(b) determining a level of binding of the first polypeptide to the second polypeptide; and

(c) comparing the level of binding to a control level of binding of the first polypeptide to the second polypeptide in the absence of candidate agent, and therefrom determining whether the candidate agent modulates BMP-mediated signaling.

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### **REMARKS**

Claims 1-10 are pending. The Examiner objected to claim 1 for containing language encompassing a non-elected species of the invention. Claims 1 and 3-10 are rejected under 35 U.S.C. § 103(a) as being obvious over cited art. Claims 1-10 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Claims 1-10 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 1 has been amended and is fully supported by the specification and claims as originally filed (e.g. page 10, the first full paragraph through page 15, the first paragraph). No new matter is introduced with these amendments.

### **Examiner's Objection to Claim 1**

The Examiner objected to claim 1 for containing language encompassing a non-elected species of invention. Claim 1 has been amended to remove the language directed to the non-elected species. Specifically, "TGF- $\beta$ - and/or" has been removed from the preamble and (c) of claim 1. Applicants respectfully submit that claim 1 is no longer directed to a non-elected species of the invention and the Examiner's objection should be removed.